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Phase II Study of Cisplatinum and Carboplatinum (CACIS) Combination in Advanced Stage Neuroblastomas

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Background. Platinum derivatives are, among others (cyclophosphamide, etoposide, doxorubicin), the most active drugs in neuroblastomas. As the combination of carboplatin (CBDCA) with cisplatinum (CDDP) was proven effective in some carcinomas, we proposed it as a second-line therapy in neuroblastoma.

Procedure. Nineteen children with neuroblastoma and primary refractory disease (seven cases) or relapse either untreated (eight cases) or resistant to second-line therapy (four cases), were treated with cisplatinum and carboplatinum (CACIS) combination. All but one patient had previously received CDDP (median 400: 200 to 1,200 mg/m^2) and 15 out of 19 had also received CBDCA (median 1,600:800 to 5,000 mg/m^2). Twelve had previously received intensification with megatherapy. The CACIS regimen included CBDCA (100 mg/m^2/day as a 1-hour infusion, for 4 days) and simultaneous CDDP (25 mg/m^2/day as a 3-hour infusion, for 4 days).

Results. Eight out of 19 patients (42%) achieved a partial response with a duration of response of 3 to 12 months (median 6). No patient achieved a complete response. The toxicity was mainly hematological, though one patient died after two courses of an interstitial pneumonia of unknown origin. Only one patient developed alopecia. The renal toxicity was low.

Conclusions. The CACIS regimen is an effective combination of platinum derivatives. It may be proposed as second line protocol, especially for children with neuroblastoma who relapse after megatherapy. Med. Pediatr. Oncol. 30:9–14, 1998.

Key words: carboplatinum; children; cisplatinum; neuroblastoma; phase II

INTRODUCTION

Neuroblastoma is the most frequent solid tumor before the age of 5 years. More than 70% of cases present with poor prognosis disease after the age of one [1]. Nowadays, the usual front-line induction therapy for patients with metastatic neuroblastoma contains an association of cyclophosphamide, doxorubicin, etoposide, and platinum derivatives (cisplatinum [CDDP] and/or carboplatinum [CBDCA]) [2–7]. Despite consolidation with megatherapy the 5-year overall survival does not exceed 30% to 40%. Relapsing patients represent a challenge, since most active drugs have been used. It has been shown that patients who relapse postmegatherapy have no chance for long-term survival with a second megatherapy [8].

There is thus a place for second-line therapy in relapsing or refractory patients. In this setting, different approaches have been proposed: therapeutic metaiodo benzyl guanidine MIBG [9], differentiating agents [10], and analgetics. However, chemotherapy protocols may still have a role at this stage. Oral etoposide [11], and phase I–II studies [12,13] may be proposed. The cisplatinum and carboplatinum (CACIS) regimen described may be an attractive alternative for these end-stage patients.

PATIENTS AND METHODS

Between June 1990 and April 1994, 19 children under 18 years of age with end-stage neuroblastoma were treated with the CACIS combination at the centre L Bérard of Lyon, CHUs of Bordeaux and Saint Etienne.

Eligibility requirements for the study included: stage III or IV neuroblastomas refractory to or relapsing after conventional therapy and creatinine clearance superior to 60 ml/min/1,73 m^2. A 4-week interval without antitumor treatment was mandatory. All patients had at least one measurable or evaluable lesion (bone, bone marrow, primary tumor, catecholamine). This protocol was approved by the ethical committee of Université C. Bernard, Lyon, France. Oral or written consent was given by the parents in the presence of a witness.

Pretreatment investigations included: complete physi

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TABLE I. CACIS Phase II Trial Results*

No.	Initial status	Previous therapy (number of cases in parentheses)	CDDP dose mg/m^2	CBDCA dose mg/m^2	Resistance to platin	Status before trial	Response (Months)	Further therapy	Outcome (Months)	Inter-course
1	IV RP BM+ BO+	OPEC (8)/SURG/ CARBO MELP ABMT/IL2 (3)	560	1,700	POTENT. SENS.	PRIM REFR PROG	PR (7)	CACIS (3)	DOD (12)	35
2	IV RP BM+ BO+	VP CDDP (6)/SURG/ IFO ADR VCR (4)/MIBG (5)/VCR (10)/VP CBDCA (2)/ANTIGD2 (1)/RT	1,200	1,600	POTENT. SENS.	PRIM REFR PROG	PR (12)	CACIS (2)/VP 16 (11)	DOD (16)	39
3	III RP	SURG/N4SE/SURG/ VP CBDCA (5)/ BCNU VM 26 CDDP ABMT1/ VCR MELP TBI ABMT2/SURG/ RT	200	5,000	POTENT. SENS.	UNTR DIST RELA	PR (9)	CACIS (1)/SURG/ RT	AWD (36+)	49
4	IV PV BM+ BO+	PEPTI (2)/CDDP (2)/VM26 ADR (4)/VP CBDCA (3)/VP CDDP (1)	400	2,400	PRIM. RES.	PRIM REFR	NR	CACIS (2)	AWD (44)	36
5	III PV	SURG/CADO (4)/VP CDDP (2)/SURG/ VP CBDCA (2)/ SURG/RT/CBDCA ADR (3)	400	2,800	SEC. RES	RESI DIST RELA	NR	MELP CBDCA ABMT/ MIBG	DOD (13)	40
6	IV RP BM+ BO+	PEPTI (2)/VP CDDP (3)/VM ADR (1)/ VCR MELP TBI ABMT/VP CBDCA (2)/MIBG (1)	600	1,600	SEC. RES	RESI DIST RELA	PD	RT	DOD (7)	50
7	IV RP BM+ BO+	VP CDDP (2)/CADO (2)/SURG/BCNU VM CBDCA ABMT1/SURG/ VCR MELP TBI ABMT2/IL2 (2)/ANTI GD2 (1)/RETINOIC ACID	400	1,250	POTENT. SENS.	PRIM REFR PROG	PR (4)	CACIS (2)	DOD (6)	36
8	IV RP BM+ BO+	CADO (2)/VP CDDP (2)/SURGERY/ BCNU VM CARBO ABMT (1)/VCR MELP TBI ABMT (2)/IL2 (1)	400	1,250	POTENT. SENS.	PRIM REFR	PD	NONE	DOD (1)	0
9	IV RP BM+ BO+	OPEC (5)/COPAD (3)/SURGERY/ VCR MEL TBI ABMT (1)/SURG/ IL2 + LAK (1)/VP CBDCA (2)/RT	350	1,600	SEC. RES	RESI DIST RELA	NR	CACIS (2)/ RETINOIC ACID/ MIBG (2)/RT/ SURG/RT	DOD (28)	42
10	IV RP BM+ BO+	CADO (2)/VP CDDP (2)/SURG/VCR MEL TBI AMBT (1)/ANTI GD2 (1)/RT	400	0	POTENT. SENS.	RESI DIST RELA	PR (6)	CACIS (3)/RT/ RETINOIC ACID/ MIBG/VP	DOD (24)	46

TABLE I. (Continued)

No.	Initial status	Previous therapy (number of cases in parentheses)	CDDP dose mg/m^2	CBDCA dose mg/m^2	Resistance to platin	Status before trial	Response (Months)	Further therapy	Outcome (Months)	Inter-course
11	IV RP BM+ BO+	CADO (2)/VP CDDP (2)/VP CBDCACADO (2)/VP CDDP (2)/SURG/VCR MEL TBI ABMT (1)	400	1,600	POTENT. SENS.	UNTR DIST RELA	NE	NONE	D TOX PI (2)	38
12	IV RP BM+ BO+	CADO (2)/VP CDDP (2)/SURG/VCR MEL TBI ABMT (1)	400	0	POTENT. SENS.	UNTR DIST RELA	PD	CACIS (2)	DOD (3)	33
13	III RP	VP CBDCA (3)/CADO (3)/SURG AND LOCAL RT	0	2,700	POTENT. SENS.	UNTR DIST RELA	PR (4)	CACIS	DOD (5)	24
14	IV RP BM+ BO+	CADO (2)/VP CY (1)/VP CDDP (2)/VP CBDCA (1)/SURG/IL2	400	800	POTENT. SENS.	UNTR DIST RELA	PD	RT	DOD (4)	0
15	IV RP BM+ BO+	PE (4)/CADO (4)	400	0	POTENT. SENS.	PRIM REFR	NR	MIBG	DOD (4)	35
16	IV RP BM+ BO+	CADO (2)/VP CDDP (2)/VP CARBO (2)/SURG/ MEL-CARBO ABMT/IL6/RT LOCAL	400	1,600	PRIM. RES.	UNTR DIST RELA	NE		AWD (2)	42
17	IV RP BM+ BO+	VPCDDP (2)/CADO (2)/VPCARBO (2)/ONC MEL TBI ALLO	400	1,600	POTENT. SENS.	UNTR DIST RELA	PR (4)	CACIS (1)	AWD (4)	27
18	IV RP BM+ BO+	VP CDDP (2)/CADO (2)/VP CARBO (2)/ONC MEL TBI ABMT	400	1,600	POTENT. SENS.	UNTR DIST RELA	PR (3)	CACIS (2)	DOD (150)	32
19	III RP	CADO (4)/PE (2)/IL6	200	0	POTENT. SENS.	PRIM REFR	NR	MELP CBDCA ABMT	AWD (5)	31

*ABMT, autologous bone marrow transplantation; antiGD2, anti-ganglioside; ALLO, allogeneic bone marrow transplantation; AWD, alive with disease; BM, bone marrow; BO, bone; CADO, cyclophosphamide, vincristin, doxorubicin; CBDCA, carboplatinum; COPAD, cyclophosphamide, vincristin, prednisone, doxorubicin; CR, complete response; DOD, died of disease; D TOX PI, toxic death due to interstitial pneumonia; GNB, ganglioneuroblastoma; histo, histology; IFO, Ifosfamide; IL2 (6), Interleukin 2 (6); INTERCOURSE, number of days between course 1 and 2; LDH, lactate dehydrogenase; MIBG, meta iodo benzyl guanidine therapy; MELP, melphalan; NB, neuroblastoma; NE, nonevaluable; NR, no response; NSE, neuron specific enolase; OPEC, vincristin, platinum; VM26, cyclophosphamide; PD, progressive disease; PE, platinum, etoposide; POTENT SENSIT, potentially sensitive; PRIM REFR, primary refractory; PRIM RES, primary resistance; PV, pelvis; PEPTI, peptichemio; RESI DIST RELA, resistant distant relapse; RP, retroperitoneal; RT, radiation therapy; SEC RES, secondary resistance; SURG, surgery; TBI, total body irradiation; UNTR DIST RELA, untreated distant relapse; VP CBDCA, VP16-carboplatinum; VP CDDP, VP16-cisplatinum; VCR, vincristine.

cal examination, complete blood count, renal and hepatic function tests, catecholamine evaluation, bone marrow smears and biopsies, MIBG scan, bone scan and measurements of lesions by ultrasonography and/or CT scan as required. Post-treatment evaluation included target reassessment. Status prior to trial was defined as follows: primary refractory if patients showed no response during first-line therapy, untreated relapse were patients who received CACIS as first rescue therapy, and refractory relapses were patients who received CACIS as further rescue therapy.

Treatment plan: patients were hospitalized for treatment. CBDCA was administered at a dose of 100 mg/m^2/d for 4 days in a 1-hour perfusion period, and CDDP at a dose of 25 mg/m^2/d for 4 days as a 3-hour infusion. The trial included two cycles with a scheduled interval of 3 to 4 weeks between each cycle. All patients received

hyperhydration of 2 l/m^2/d of 5% dextrose solution over 12 to 24 hours with 4 g NaCl/l and added potassium chloride (2 g/l) and magnesium as required.

The result of serum creatinine collected 1 month after the second course of CACIS was compared to baseline values, and the ratio was expressed as percentage of raise over the baseline value.

Evaluation of Response

The response was defined after the second cycle of CACIS, with the exception of progressive disease after one course. A complete response (CR) was defined as the disappearance of signs of tumor in both primary and metastatic sites. A partial response (PR) was defined as more than 50% reduction in both primary and metastatic sites for at least 4 weeks without appearance of new lesions. Any regression of tumor <50% was considered as no response (NR). Progressive disease (PD) was characterized by more than 25% increase in the size of measurable lesions at any involved site and/or appearance of new lesions. A CR in metastatic sites and a PR in the primary tumor (or vice versa) or a PR in metastatic sites and a NR in the primary tumor (or vice versa) was considered as a PR overall.

As described previously [14], patients were considered as potentially sensitive to platinum derivatives if they had shown a response to the last platinum-containing regimen received prior to this phase II study. They were considered as potentially resistant otherwise.

Patient Characteristics

Patient characteristics are summarized in Table I. Briefly, sex ratio was 8 females/11 males, ages 36 to 183 months at diagnosis (median 54), and 49 to 216 months at trial (median 80). Three patients had a ganglioneuroblastoma at time of last surgical evaluation and 16 had a neuroblastoma. The primary site was retroperitoneum in all but two patients (pelvis). Status at trial was as follows: seven were primary refractory, eight patients were untreated distant relapses, and four had a refractory relapse. Prior chemotherapy regimens had included CDDP in all but one patient (range 200 to 1,200 mg/m^2), with a median of 400, and CBDCA in 15 out of 19 patients: 800 to 5,000 mg/m^2 with a median of 1,600 mg/m^2. Twelve patients had previously received megatherapy (11 autologous including three with a double graft, and one allogeneic). Thirteen of 17 patients evaluable for response to CACIS were potentially sensitive and four potentially resistant to platinum derivatives.

RESULTS

Out of 19 patients who entered the study, the response was evaluable in only 17. One patient received additional radiation therapy on the primary site. Another patient died of toxicity prior to evaluation. Four patients showed progression after one (two patients) or two (two patients) courses of CACIS.

No patient achieved a complete response. Eight out of 19 patients (42%) achieved a partial response, with a duration of response ranging from 3 to 12 months (median 6 months). Responses were obtained in 3/8 primary refractories, 4/7 untreated relapse and in 1/4 resistant relapses and 2/7 patients who were not submitted to megatherapy previously. Responders to CACIS had previously received more CDDP (445 versus 394 mg/m^2) and CBDCA (1,913 versus 1,116 mg/m^2). Five patients showed no response after two courses of CACIS. Moreover, eight of 14 patients with tumors potentially sensitive to platinum derivatives showed a partial response, versus none of the primary (two) or secondary (three) resistant patients.

Overall survival after trial ranged from 2 to 44 months (median 5), but most patients received additional treatment. Fourteen patients died of disease, one of undocumented interstitial pneumonia while in aplasia after his second course. Five patients are alive (2 to 44 weeks, median 5), all with progressive disease.

Toxicity and Tolerance

Thirty-six courses are evaluable for toxicity: two patients received only one course due to progression. Most of the patients presented mild to moderate nausea and vomiting. Only two had WHO grade 4 digestive toxicity. In 16/30 evaluable courses, there was a WHO grade 4 neutropenia, and in 21 a WHO grade 4 thrombopenia. Transfusional support was required in most patients: red blood cells in 24/35 evaluable courses (1 to 5 transfusions), and platelets in 25/35 (1 to 8 transfusions, median: 3). The mean interval between course 1 and 2 was 36 days (24 to 50) due to hematological delay in recovery.

One patient only had severe deterioration of auditory function. However, this girl had previously received 350 mg CDDP and 1,600 mg CBDCA and a total body irradiation.

The mean percentage of creatinine increase over baseline value was 2% (median 0%, extreme −45 to 93%). No patient developed acute renal failure during the trial. However, one patient required dialysis after six courses: this patient had previously received a high dose of platinum derivatives (CDDP: 560 mg/m^2 and CBDCA 1,700 mg/m^2), and received six further courses of CACIS (i.e., CDDP: 600 mg/m^2 and CBDCA 2,400 mg/m^2). The renal failure may thus be attributed to the cumulative dose of platinum derivatives.

Four patients presented with infectious complications: one an oral herpetic infection, otits media, sinusitis, and a lethal interstitial pneumonia. The latter patient presented with a diffuse undocumented interstitial pneumo-

nia and ultimately died despite respiratory support 2 months after initiation of trial. He had previously received a total body irradiation (TBI) containing regimen that may explain the symptoms. No patient developed signs of neurological toxicity. Only one child (who had previously received TBI) had alopecia.

DISCUSSION

There are several reasons to propose a therapeutic interaction between CDDP and CBDCA. In animal models and in vitro, CDDP and CBDCA have a similar spectrum of antitumoral activity [15] and are usually cross-resistant [16]. However, in neuroblastoma as well as in other malignancies, a lack of cross-resistance has been suggested [17]. These two derivatives have different toxicities that are not overlapping: CDDP induces renal damage, neurotoxicity, and digestive toxicity, whereas the major toxicity of CBDCA is myelotoxicity. Moreover, the pharmacokinetics of these drugs are also different: CDDP is bound to proteins and its active moiety is cleared primarily by extrarenal mechanisms, whereas CBDCA is less bound to proteins, and mainly cleared through renal excretion [18]. A phase II randomized trial was conducted in patients with advanced non-small-cell lung cancer to determine if the combination of moderate-dose cisplatin and carboplatin could avoid the long-term limiting (renal, auditory, neurologic) toxicity of high-dose cisplatin. Although there was no difference between the arms for alopecia, emesis, and leukopenia, the combined arm was significantly associated with more thrombocytopenia (although rarely severe) and, more importantly, with less renal (19% vs. 36%), auditive (4% vs. 16%), and neurologic (0% vs. 16%) toxicity of any grade [19].

Several studies showed the efficacy of the association of CDDP and CBDCA in ovarian carcinomas, head and neck cancer, lung cancers [19–25]. Two different schedules were proposed. The first used simultaneous injection of both drugs over 1 day, which induced more toxicity, without significant advantage on efficacy as compared to CDDP alone [21,24,26]. This increased toxicity may be due to an augmentation of the area under the curve [27]. The second schedule included sequential administration of the drugs over 2 days, with less toxicity [23,28]. However, in a randomized trial no significant improvement of activity has been obtained by the addition of CBDCA to CDDP-containing regimen [19].

Our study suggests that even in patients who previously received platinum, there may be a place for platinum sensitivity. The 42% response rate reported is inferior to that described in previous reports with VP 16-high dose cisplatinum (55% of which 22% were CRs) [5], or VP16-carboplatinum (43% of which 10% were CRs) [17], as no complete response was obtained in this CACIS phase II trial. However, the patients in the current report had been more intensively treated as they had all previously received platinum derivatives. The lack of activity in patients who previously showed platinum resistance has been demonstrated in other malignancies [29], and suggests that this combination should not be used in such situations.

There was no renal toxicity after two courses, despite high cumulative doses of platinum previously received, since only one in eight evaluable patients had a 50% rise in seric creatinine. The audiologic toxicity was not clinically evident, except in one patient. Hematological toxicity was heavy, but most patients were heavily pretreated. Despite its financial cost, the lack of alopecia (except in one patient) is a strong argument to support the use of this treatment in relapsing patients if the chance for a long-term survival is weak. It should be mentioned, however, that a 4-day in-patient hospitalization may represent a burden in these end-stage patients, though the lack of home-based treatment may represent an advantage.

The activity and toxicity of CACIS regimen are less than that of previously published regimens, but it was delivered to patients who relapsed after having received platinum derivatives. It may thus be used either as a second-line therapy for the patients with a chance for definitive cure, or as a palliative treatment in patients who have received all the drugs known to be active in neuroblastoma [30].

REFERENCES

1. Hartmann O, Slopinario M, Tournade MF, et al.: Neuroblastomes traités à I'Institut Gustave Roussy de 1979 à 1979. Cent soixante treize cas. Arch Fr Ped 40:15–21, 1983.
2. Bernard JL, Philip T, Zucker JM, et al.: Sequential cis platin/VM 26 and vincristine/cyclophosphamide/doxorubicin in metastatic neuroblastoma: An effective non cross resistant regimen? J Clin Oncol 5:1952–1959, 1987.
3. Hartmann O, Pinkerton CR, Philip T, et al.: Very-high dose cisplatin and etoposide in children with untreated advanced neuroblastoma. J Clin Oncol 6:44–50, 1988.
4. Kushner BH, O'Reilly RJ, Mandell LR, et al.: Myeloablative combination without total body irradiation for neuroblastoma. J Clin Oncol 9:274–279, 1991.
5. Philip T, Shalie R, Pinkerton R, et al.: A phase II study of the high dose cisplatin and VP16 in neuroblastoma: A report from the Société Française d'Oncologie Pédiatrique. J Clin Oncol 9:941–950, 1987.
6. Philip T, Zucker JM, Bernard JL, et al.: Improved survival at 2 and 5 years in the LMCE1 unselected groups of 72 children with stage IV neuroblastoma older than 1 year of age at diagnosis: Is cure possible in a small subgroup? J Clin Oncol 9:1037–1044, 1991.
7. Pole JG, Casper J, Elfrenbein, et al.: High dose chemoradiotherapy supported by marrow infusion for advanced neuroblastomas: A pediatric oncology group study. J Clin Oncol 9:152–158, 1991.
8. Ladenstein R, Lasset C, Hartmann O, et al.: Impact of megatherapy on survival after relapse from stage 4 neuroblastoma in

patients over 1 year of age at diagnosis: A report from the European Group for Bone Marrow Transplantation. J Clin Oncol 11: 2330–2341, 1993.
9. Hoefnagel CA, Voute PA, De Kraker J, et al.: [131I]metaiodobenzylguanidine therapy after conventional therapy for neuroblastoma. J Nucl Biol Med 35:202–206, 1991.
10. Smith MA, Adamson PC, Balis FM, et al.: Phase I and pharmacokinetic evaluation off all-trans-retinoic acid in pediatric patients with cancer. J Clin Oncol 10:1666–1673, 1992.
11. Davidson A, Lewis I, Pearson ADJ, et al.: 21-day schedule oral etoposide in children—a feasibility study. Eur J Cancer 29A: 2223–2224, 1993.
12. Hurwitz CA, Relling MV, Weitman SD, et al.: Phase I trial of Paclitaxel in children with refractory solid tumors: A pediatric oncology study group. J Clin Oncol 11:2324–2329, 1993.
13. Pratt CB, Stewart C, Santana VM: Phase I study of topotecan for pediatric patients with malignant solid tumors. J Clin Oncol 12: 539–543, 1994.
14. Markman M, Hoskin W: Response to salvage chemotherapy in ovarian cancer: A critical need for precise definitions of the treated population. J Clin Oncol 10:513–514, 1992.
15. Prestayko AW, Bradner WT, Huftalen JB, et al.: Antileukemic (11210) activity and toxicity of cisdiamminedichloroplatinum (II) analogs. Treat Cancer Rep 63:1503–1508, 1979.
16. Hamaguchi K, Godwin AK, Yakushiji M, et al.: Cross-resistance to diverse drugs is associated with primary cisplatin resistance in ovarian cancer cell lines. Cancer Res 53:5225–5232, 1993.
17. Frappaz D, Michon J, Hartmann O, et al.: VP16-carboplatin in neuroblastoma: A SFOP phase II study. J Clin Oncol 10:1592–1601, 1992.
18. Newell DR, Pearson AD, Balmanno K, et al.: Carboplatin pharmacokinetics in children: The development of a pediatric dosing formula. The United Kingdom Children's Cancer Study Group. J Clin Oncol Dec 11:2314–2323, 1993.
19. Sculier JP, Klastersky J, Giner V, et al.: Phase II randomized trial comparing high-dose cisplatin with moderate-dose cisplatin and carboplatin in patients with advanced non-small-cell lung cancer. European Lung Cancer Working Party. J Clin Oncol 12:353–359, 1994.
20. Cavalli F: Phase I study of the combination of weekly cisplatin (CDDP) and monthly carboplatin (CBDCA). Proceedings ASCO. J Clin Oncol 9: Abstract 310, 1990.
21. Dimery I, Winn R, Christian M, McCarthy K, Hong W: Combination therapy with carboplatin (NSC 241240) plus cisplatin in recurrent squamous head and neck carcinoma. Proceedings ASCO. J Clin Oncol 9: Abstract 690, 1990.
22. Gill I, Muggia FM, Terheggen PM, et al.: Dose-escalation study of carboplatin (day 1) and cisplatin (day 3): Tolerance and relation to leukocyte and buccal cell platinum—DNA adducts. Ann Oncol 2:1115–1121, 1991.
23. Lund B, Hansen M, Hansen HH: High dose platinum consisting of combined carboplatin and cisplatin in previously untreated ovarian cancer patients with residual disease. J Clin Oncol 7:1469–1473, 1989.
24. Powell BL, Stanley V, Brockschmidt J, et al.: Combination of carboplatin and cisplatin for advanced squamous carcinoma of the head and neck. Proceedings ASCO, J Clin Oncol 9: Abstract 693, 1990.
25. Saito H, Shimokata K, Saka H, et al.: Phase II study of carboplatin, cisplatin, and vindesine in advanced non-small-cell lung cancer. Cancer Chemother Pharmacol 33:154–156, 1993.
26. Hardy J, Wiltshaw E, Blake P, et al.: Cisplatin and carboplatin in combination for the treatment of stage IV ovarian carcinoma. Proceedings ASCO. J Clin Oncol 9: Abstract 643, 1990.
27. Trump DL, Grem JL, Tutsch KD, et al.: Platinum analogue combination therapy: Cisplatin and carboplatin. A phase I trial with pharmacokinetic assessment of the effect of cisplatin administration on the carboplatin excretion. J Clin Oncol 5:1281–1289, 1987.
28. Sessa C, Martinelli G, Goldhisrsch, et al.: Phase I study of the combination of the combination of weekly cisplatin and monthly carboplatin with dosage adaptation to renal function. Proceedings ASCO. J Clin Oncol 9: Abstract 308, 1990.
29. Grabois M, Frappaz D, Bouffet E, et al.: High-dose VP16 cisplatinum in soft tissue sarcoma of children. Cancer Chemother Pharmacol 33:355–357, 1994.
30. Cheung NKW, Heller G, Kushner BH, et al.: Stage IV neuroblastoma more than one year of age at diagnosis: Major response to chemotherapy and survival durations correlated strongly with dose intensitivity. In Evans AE, D'Angio GJ, Knudson AG, Seeger RC (eds.), Wiley-Liss, Inc., NY. Adv neuroblastoma Res 3:567–573, 1991.